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(57) Abstract

A moldable bone-implant material containing between about 40%-58% hard filler particles and of between 15%-60% of a biocompatible, biodegradable inorganic, binder. The binder comprises calcium sulfate hemihydrate. A preferred hard filler is hydroxyapatite. In use, the material is applied under conditions which allow molding and the bone site is filled with the modable material, which then forms a contour-fitting, semi-rigid implant. The implant retains its contour fit and acquires a rigid final state as the binder in the implant is gradually biodegraded and replaced through tissue ingrowth from the surrounding bone site.

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MOLDABLE BONE IMPLANT MATERIAL

The present invention relates to a moldable bone-implant material formed of hard bone graft filler particles bound together into a moldable cohesive mass with a biodegradable substrate.

Background of the Invention

Bone implants are used for bone reconstructive surgery and repair where bone loss or traumatic damage has occurred. In addition to the usual function of strengthening and filling in a repaired bone area, implants can also act to transmit forces to the surrounding bone area, to preserve the vitality of the bone. As an example of the latter function, bone implants are commonly placed in tooth-extraction sites by to help preserve the alveolar bone by providing for continued force on the bone during chewing.

The most proven and accepted synthetic material for bone reconstruction and repair is hydroxylapatite. This material has outstanding biocompatibility, due to its similarity in composition and crystalline structure to the inorganic component of bone. The most important property of hydroxylapatite is its ability to bond directly to bone tissue. Tissue ingrowth into the matrix of the particles acts to stabilize the implant in the surrounding bone and, where the implant is formed of hydroxylapatite particles, forms a tissue matrix which helps maintain the integrity of the implant.

One type of hydroxylapatite implant which has been used heretofore is a rigid implant which is intended to be machined by the surgeon or dentist to fit the implant site. The implant may be formed of a solid dense block or porous block of hydroxylapatite or by binding hydroxylapatite particles with a permanent, rigidifying polymer material.

Implants of this type suffer from a number of disadvantages. The process of determining the shape of the bone site and fashioning the implant to fit the site is time consuming and complicates the surgery. The implant rarely is ideally shaped and therefore may work loose in the site before tissue ingrowth can occur. Such implants require suturing soft tissue to hold them in place, and may require protecting the site against movement for an extended post-operative period. Also, the implant cannot be fashioned to take advantage of undercut surfaces at the bone site which otherwise might contribute to anchoring the implant. Up to 90% of such implants have been reported to work loose within the first year of implantation.

Implants formed of loose non-bonded hydroxylapatite particles are also well known in the prior art. In preparing an implant of this type, the particles are wet with saline or the patient's blood to give the particles some cohesion and make them manageable during the implant procedure. The loose mass of particulate material is placed in the bone site, where it can adapt to the contours of the surrounding support tissue. After implantation, the particle mass is ingrown with hard or soft tissue which stabilizes the mass of particles, typically in a period of a few days to weeks. The implant can thus acquire a rigid contoured fit, and can also conform to undercut regions in the site to provide increased anchorage.

Despite the advantages of loose-particle implants, a number of problems have been encountered. Loose particles are generally difficult to deliver to the site in a convenient manner, and paraphernalia, such as mixing dishes, applicator funnels, suction devices, and the like, may be required. The particle mass has little cohesive strength and very often loses its shape before the mass is stabilized by tissue ingrowtn. For example, particles

used for rebuilding the alveolar ridge often exhibit ridge flattening and hence a loss of ridge height before the implant particles can be stabilized by tissue ingrowth. The loose cohesion of the particle mass also allows particles to migrate away from the implant site before tissue ingrowth is complete, and this can result in implant failure and exfoliation of particles into the patient's mouth in the case of oral implants.

SUMMARY OF THE INVENTION

It is a general object of the invention to provide a bone-implant material which substantially overcomes problems associated with existing solid rigid-block and loose particle types of implant materials.

A more specific object of the invention is to provide such material which overcomes the disadvantages of loose-particle implant placement, including loss of implant material and shape, while maintaining the contour-fit and exceptional bone-like and biological ingrowth characteristics of particulate hyroxylapatite.

A related object of the invention is to provide such a material which is readily molded to fit the contours and undercut regions of a bone implant site.

Still another object of the invention is to provide a method using such material for filling a bone site with a rigid, contour-fitting, hydroxylapatite implant.

In accordance with the invention, the binders which can be used in the present moldable bone-implant materials comprise inorganic materials. Inorganic materials can include those materials which when placed in a bone-implant environment (a) are compatible with that environment, (b) undergo biodegradation in that environment to release only biocompatible degradation

products, and (c) undergo biodegradation at a rate which allows gradual binder replacement in the material by in situ tissue ingrowth over a several-day to several-week period. Among suitable inorganic binders, inorganic cements are preferred, with special preference being given to calcium sulfate hemihydrate as it can consistently yield an implant material which will have the desired moldability properties while allowing gradual binder replacement in the material by in situ tissue ingrowth over a several-day to several-week period. The binder preferably constitutes no more than about one-third of the total solid volume of the material. When the binder biodegrades, its space becomes a void in the material which can accommodate tissue ingrowth. The minimum amount of binder is that necessary to give easy formability and provide sufficient particle cohesion and shape retention and implant strength during the period of tissue ingrowth.

In another aspect, this invention provides a storable dry bone-implant material which is made up of the filler particles in admixture with particulate inorganic cement in precure form.

In yet another aspect, this invention provides a method of filling a bone site with a contour-fitting rigid particle bone implant. In this method of the invention, the bone-implant material comprises hard filler particles and a binder and is moldable at the conditions and time of implanting. The site is filled with the moldable material to form a contour-fitting implant in the site. Over a period of several days to several weeks or more, the binder undergoes gradual biodegradation and is replaced by ingrowth of surrounding tissue. The moldable implant material may be dispensed from any convenient device or form such as syringe, tube-type dispenser, dish, or in soft block or roll form. The mold-in-place implant substantially retains its contour-fitting shape during the several-day to several-week period when the binder is

gradually degraded and replaced by tissue ingrowth from the surrounding bone site, to rigidify the implant.

These and other objects and features of the invention will become more fully apparent from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The Implant Material and its Preparation

The bone-implant material of the invention is prepared by mixing hard bone-graft filler particles with biocompatible biodegradable binder. The resulting material is moldable, allowing the material to be applied to a bone site in a contour-fitting manner. The terms "biocompatible" and "biodegradable" as used herein have their normal art-accepted meanings, that is, "biocompatible" means that material is compatible with a living animal and in use does not give rise to untoward effects, reactions, toxicity or the like; and "biodegradable" means that a material undergoes an expected breakdown in its physical or chemical structure when exposed to a given biological environment of use.

Filler Particles

Any biocompatible inorganic hard filler particles, including autogenous bone chips, can be used in this invention. However, hydroxylapatite is the preferred filler for its permanence and biological profile. Tricalcium phosphate (TCP) and calcium phosphate glass granules may also be used alone or in combination with hydroxylapatite, particularly if some degree of resorption is desired in the filler.

Hydroxylapatite particles are preferably the type of dry free-flowing hydroxylapatite particles supplied for use in

forming wetted, loose-mass implants, and can be obtained commercially from Orthomatrix Corporation (Dublin, CA) or Calcitek (San Diego, CA). Particle sizes of between about 250 and 5000 microns are generally suitable and particle sizes between 250 and 2000 microns are preferred, smaller particles showing increased difficulty in allowing tissue ingrowth and larger particles requiring increased quantities of binder for ease of application. As marketed by Orthomatrix Corporation, these particles are supplied as ranges of various sized particles, for example from 250-550 microns (HA-500), 500-1000 microns (HA-1000), and the like. Such mixtures are quite suitable.

Binder

The binder used in forming the bone graft material is selected for three important properties: (a) susceptibility to rapid biodegradation, to allow for gradual binder replacement by tissue during tissue ingrowth, without retarding ingrowth; (b) flowability or fluid-flow properties in combination with cohesiveness so as to allow the material to be molded and formed during implantation and achieve a contour fit at the bone site; and (c) biocompatibility, that is, the binder should not provoke a serious inflammatory or other tissue-rejection response, at lease within the several-week period when tissue ingrowth replacement is occurring.

For most biodegradable inorganic binders of interest, biodegradation may involve gradual dissolution of a moderately soluble inorganic salt, hydrolysis of bonds within an inorganic structure or ionization of weakly acidic or basic groups within the inorganic material. Preferred binders are those which are degraded to metabolites which are normal to the body or for which the body has effective elimination routes.

Examples of preferred inorganic binders include the inorganic cements such as the gypsum-based plasters including calcium sulfate hemihydrate (Plaster of Paris), sodium based Mack's cement and the like. These inorganic materials are characterized by forming a cohesive plastic mass when mixed with an aqueous liquid such as water, sterile water, sterile saline, patient's blood or the like, and through hydration taking a "set". Of these materials, calcium sulfate hemihydrate is generally preferred because of its long acceptance. (See, for example, Peltier, Leonard. F, CLINICAL ORTHOPAEDICS, Vol. 21, Pages 1-31, 1961) as a safe restorative material, as well as its properties of being plastic and moldable for useable periods before it "sets up" and of being bioerodible at rates consistent with the biodegradability requirements of this invention. The calcium sulfate hemihydrate can be in either the alpha or beta crystal form. It is readily available commercially such as the material marketed as Durobond Plaster of Paris. More specialized forms of calcium sulfate hemihydrate can be used as well, with special preference being given to materials such as Baker Chemical Company's calcium sulfate hemihydrate which appears to yield a stronger product at lower binder use levels and thus a product with less volume loss as its calcium sulfate is biodegraded.

The moldable, plastic nature of the inorganic binders is advantageous in the present invention for several reasons. The inorganic cement type binders provide implant materials that may be hand formed as a relatively low-viscosity mixture when initially mixed with the aqueous liquid and then shortly thereafter, e.g. in a matter of from 3 to 45 minutes, assume a relatively high viscosity, more rigid shape when the cement sets. These binders allow a cohesive mass of implant material to be formed and used and shaped. This corrects the problems of particle migration which occur when simple suspensions of powders are employed. Also, materials using the inorganic

cement binders provide plasticity and moldability only during the implantation procedure so that the material, once implanted in a bone site, retains a more rigid, shape-retaining condition.

The binder preferably ranges in fluid-flow properties (flowability) between a highly viscous fluid and a puttylike semi-solid, at the selected conditions of use. With too low a binder viscosity, the implant material suffers the same problems seen in loose-particle implants: poor shape retention, once molded, and poor cohesiveness, leading to exfoliation of particles before or during the tissue ingrowth period.

Advantages of the Invention

It is important to recognize that the binders described here do not rely on highly exothermic chemical reactions to produce a rigid mass as is commonly done with thermosetting polymers such as polymethylmethacrylate (PMMA). Thermosetting polymers generally require initiators to catalyze hardening and such reactions are exothermic. Where PMMA is used, it can generate enough heat to damage adjacent tissue. Accordingly, the binders employed in this invention are at most only mildly exothermic when they set up and do not damage adjacent tissue. Thermoset polymers also contain residual unpolymerized monomer which, along with catalyst residue, give material of questionable and variable biocompatibility. Also, the moldability of thermoset binders is time dependent and not reversible, or reformable once hardened.

The implant materials of this invention have the following desirable characteristics:

1. Formability, moldability - and the ability to completely fill undercut cavities not possible with solid blocks or composites.

2. They are, during application, two phase materials.

3. The binder is biocompatible and biodegradable.

4. The solid particle phase is discontinuous and the size and shape of the solid particles determines and presents a unique pore structure for tissue ingrowth.

5. The binder is the continuous phase.

6. The binder's function is temporary for ease of application of the implant and to hold the particles in place for a limited period after implantation until the binder is replaced by tissue.

The binder-containing implant materials are generally formed in two steps. In the first step, the filler particles are blended with a dry particulate form of the binder. In the second step, the dry mixture is mixed with a pharmaceutically acceptable aqueous liquid, most typically sterile water, sterile saline or the patient's blood to yield the desired cohesive, moldable, plastic mass. This material is then applied as the desired implant and allowed to stand for a few minutes, i.e. from about 1 to about 30 minutes, and preferably from about 5 to 30 minutes, during which time it sets or solidifies into a relatively rigid body.

The ratio of particles to binder, the amount of aqueous liquid added and the amount of mixing applied can each have an effect on the properties of the moldable plastic implant material and the final "set" product.

Typically, the proportions of dry filler particles to dry binder ranges from the largest proportion of filler that will give a moldable cohesive product, (generally about 85-90% by weight filler and 10-15% binder) down to the smallest proportion of filler that will give a product that will still deliver an adequate amount of solid filler to the bone area being repaired to achieve the desired repair (generally about 30-40% filler and 60-70% by weight binder). As hydroxylapatite makes up the filler particles, it is of special advantage to use a mixture that provides at least 2/3 of the mixture volume as filler, as this permits the defined level of voids between the filler particles to permit the fortuitous growth of bone tissue into the particle matrix, more preferably so that from 70% to 95% of the volume is hydroxylapatite. A preferred range of proportions of the mixture of hydroxylapatite and calcium sulfate hemihydrate comprises from 85-40% by weight of the former and from 15-60% by weight of the latter. A more preferred set of proportions are hydroxylapatite 55-75% by weight and especially 60-70% by weight, and calcium sulfate 24-45% by weight and especially 30-40% by weight.

The amount of aqueous liquid added to form the plastic mass should be controlled. If the weight of aqueous liquid is substantially greater than about 25% of the weight of filler plus binder, a product will result which is syrup-like and difficult to apply. If the weight of water is as low as 5% or so, the resulting product will not be properly plastic and cohesive, although it may be useable for repairing minor bone defects or holes such as filling tooth extraction sites, or like defects, where it can be tightly packed into the defect and its lack of coherence will not be a critical failing. Preferred aqueous liquid levels are from about 10 to about 22% by weight based on the weight of the dry components, and most preferred aqueous liquid levels range from about 15 to about 20%.

The mixing time should also be monitored. As a general rule, the longer the mixing time between the aqueous liquid and the dry powders, the shorter the working time before the plastic mixture sets up into its rigid form. Generally, it is not realistic to expect the mixing to be complete in less than about 10 seconds. If it is extended longer than about 2 minutes, this can decrease the set-up time to a minute or two. Best results are generally achieved when the mixing time is from about 15 seconds to about 90 seconds, with special preference being given to mixing times in the range of from about 20 seconds to about 45 seconds.

A detailed description of the preparation and use of the inorganic binder-containing bone implant material of the invention is provided in the Examples, together with data demonstrating its advantageous properties.

After application of the inorganic binder-containing materials to the bone-implant site, it is generally preferred to allow the material to set for a brief period, such as from about 5 minutes to about 30 minutes, so as to allow the binder to fully cure and form a strong rigid body.

As noted previously, the implant materials of this invention may contain other added materials such as markers or the like, if desired.

The bone-implant material may be presterilized by heat, gamma radiation, ethylene oxide, or other available methods. For dispensing, the material can be supplied in a syringe or squeeze-bottle container, allowing direct application of the material into the bone site. Alternatively, the material can be supplied in dish, or flexible roll or block form.

Bone Implant Method

This invention includes a method for forming a rigid contour-fitting hard filler implant in a bone site. The method is generally applicable to bone reconstruction or repair needs where a hydroxylapatite or other hard filler bone implant can strengthen a bone region and/or act to transmit stresses to surrounding bone area, to preserve the vitality of bone. Typical applications include replacing damaged or resorbed bone regions, repairing bone fractures, and filling tooth-extraction sites to help preserve underlying alveolar bone. In addition, the method may be used in anchoring a joint-replacement prosthetic device within a suitable bone cavity.

The bone site which is to receive the implant is prepared by conventional surgical techniques. These usually involve exposing and cleaning the bone site, and may require surgical removal of parts of the bone, for example, to form undercuts at the bone site or to shape the site for more favorable implant seating or stress transmission. For attaching a prosthesis which is designed to be anchored to the bone through a stem, the bone is prepared with a suitable stem-receiving cavity. Here the space between the bone cavity and the prosthesis stem forms the bone site which is to be filled with the implant material.

In practicing the invention, there is provided a moldable hydroxylapatite containing bone-implant material of the type above. As described above, inorganic binder-containing implant materials having a range of molding temperatures and conditions and varying rates of biodegradability can be provided, by adjusting the composition and amount of binder in the material. Naturally, it is desirable to use proportions of binder which will assure adequate strength and cohesiveness.

Also as discussed above, the composition and amount of binder can be adjusted to allow for effective tissue ingrowth in the implant material. For example, if the binder is expected to be degraded only slowly at the bone site, due to lack of enzymes, body fluid flow or the like, it may be advantageous to provide increased void spaces in the material, by reducing the amount of binder. Similarly, where rapid binder breakdown is expected, a greater amount of binder would be indicated.

To prepare the binder-containing bone implant materials of the invention for use, the material is formed into its cohesive moldable form in a suitably sterile mixing zone.

To form the implant, the moldable implant material is applied to the bone site to fill the site in a preferably space-filling manner, producing a contour fit between the bone and implant. For the usual bone reconstruction and repair, the material is applied to the bone surface and pressed into or onto the site to force the material into any surface irregularities of the site, such as cracks, holes, and particularly undercut features. The outer surface of the material is then fashioned to give the bone site the desired surface appearance. The latter process may require filling the site with additional material and/or cutting away originally applied material.

In applying the method to a prosthetic attachment, the molded material is applied to the outer surface of the prosthesis stem and/or to the inner surface of the bone cavity, in an amount calculated to fill the space between bone and cavity. The stem is then forced into the cavity until the prosthesis is fully seated in the cavity and the implant material is forced substantially completely into the stem/bone space. Where the stem is relatively long, as is the case with the usual femural-side hip-joint replacement prostheses, it is generally advantageous to form a biological bond between bone and stem only in the

proximal region of the stem. In this situation, the bone site to be filled with the implant material would be confined to the proximal stem/bone space.

The method of the invention is effective to produce a rigid, contour-fitting implant at the bone site. Unlike solid implants which have been used heretofore, implant rigidity is produced by tissue ingrowth and replacement of binder, and the binder itself only provides initial cohesivenss and semi-rigidity. As mentioned above, the tissue ingrowth typically occurs over about a three day to six-week period, and can involve tissue ingrowth into the void spaces of the material as well as biodegradation of the binder.

From the foregoing, it can be appreciated how various objects of the invention are met. The implant material is easily applied in moldable form to a bone site, to provide a contour-fitting implant. The method of filling the bone implant with the moldable material avoids the problems of measuring and shaping a rigid-block implant, leads to a better fit than can be achieved with solid implants, and can take advantage of undercut surfaces within the bone site.

At the same time, the material is sufficiently cohesive to resist particle exfoliation during the tissue ingrowth period, and can be made relatively rigid, after cooling, to maintain its contoured shape until it can be rigidified by tissue ingrowth. Through these advantages, the material substantially overcomes problems associated with loose-particle implants.

The invention will now be shown in the following Examples. These are presented to illustrate the invention and are not to be construed as limiting its scope.

EXAMPLE I

In a representative preparation, hydroxylapatite (Orthomatrix HA 500, 250-500 microns particle size) and calcium sulfate hemihydrate (Durobond Plaster of Paris) are mixed as dry powders in the weight ratio of 65% HA 500 - 35% Durobond until homogeneous. A 3 gram sample of this material is placed into a mixing palette. Sterile saline, 0.48-0.60 cc, is then added and quickly mixed into the powder to give cohesive, moldable, plastic bone-implant material. The material is putty-like in consistency. Mixing is completed in about 30 seconds.

The material is loaded into a syringe using a vibrator. The syringe is vibrated and its open nozzle is placed in the moldable material. The plunger is withdrawn to draw material into the syringe. The material can then be dispensed into a bone site in need of restoration. After about 5 minutes, the inorganic binder sets up into a somewhat rigid body. Prior to that time, the material can be molded and shaped into the desired contours. After an additional period, the implanted material takes on additional rigidity to serve as a rigid bone implant.

This preparation is repeated numerous times varying the relative proportions of binder and filler, the nature of the binder and the filler, the mixing time, and the nature and amount of added aqueous fluid. The materials so produced are tested to determine their physical properties and the effect of the varied parameters as follows:

A series of mixtures of hydroxylapatite (500-1000 micron size) with calcium sulfate hemihydrate (Durobond-Plaster of Paris) were prepared. The proportions of the two solids were varied from 20% calcium sulfate hemihydrate to 30%, to 35%, to 90%. These mixtures were prepared into moldable bone defect repair materials by adding water, and were cast into 1.25 cm diameter test cylinders for

compression strength tests. It was seen that the 90% sample failed at a stress of 8.2 MPa, the 40% material had the same strength and the 35% was similar, at 7.4 MPa. The 20% material failed at less than 2 MPa.

Repeating, using purer Baker Chemical Company calcium sulfate hemihydrate, 40% and 35% binder content materials had virtually identical compression strengths of about 13.3-13.6 MPa.

A similar test with Baker calcium sulfate hemihydrate and hydroxylapatite having a 250-500 micron size showed that at 40% by weight binder, the strength was 10.9 MPa, at 35%, strength was 11.4 MPa while at 30%, strength fell at 6.5 MPa. These values compare favorably with the 7-70 MPa strength range of porous hydroxylapatite and as such, show that the material of this invention can be used in applications which call for porous hydroxylapatite blocks.

Either water or saline may be used to wet the mixed calcium sulfate hemihydrate and hydroxylapatite powders without affecting the maximum attainable strength of the cured implant. The difference between the two lies in the mixing/working time constraints. A mixing time of no more than 30 seconds to give a working time of 4 to 10 minutes was typical of the results obtained when sterile saline (0.9%) was used to wet the composite. However, if sterile water was used with a 30 second mixing, the working time ranged from 20 to 30 minutes. The working time could be decreased by increasing the mixing time. Since, sterile saline is readily available, it is the preferred wetting agent. Water may be used where a delayed setting time is desired.

A 35% Baker Chemical calcium sulfate hemihydrate-hydroxylapatite composite was allowed to set hard and then the compressive strength of the composite was tested wet, following a soak of a specified number of days. Equally important as the strength was the surface erosion which

occurred, the number of loose particles resulting form the erosion and the maintenance of the set shape.

Following setting, cylinders of composite were suspended in a flask containing saline at 37°C. The flasks were placed in a shaker bath and the saline was changed every 24 hours. Samples were removed and tested at 1, 2 and 4 days. The results of this testing are shown in the following table.

STRENGTH LOSS ON SOAKING

Days of Soak	Strength MPa	Percentage Original Strength Lost
0	11.4	0
1	8.3	27.2%
2	6.1	53.5%
4	5.2	54.3%

During the first two days, there was a significant drop in strength, after which time, the rate of strength loss significantly decreased. Surface erosion began immediately upon suspension in saline, however, there were very few loose particles until 4 days of soaking had occurred. The set composite maintained its shape throughout the course of the study.

At the end of 4 days, soft tissue ingrowth would be expected to have advanced sufficiently to hold all particles in place, thereby preventing migration.

An In Vitro test of resorbtion volume was carried out as follows:

A five gram sample of dry (65 wt % HA-500/35 wt % $CaSO_4$) was wetted with saline. It was placed into a centrifuge tube and vibrated to remove air bubbles. The five gram

mixture filled the centrifuge tube to a volume of 2.9 cc. The amount of HA-500 in the five gram HA cement mixture (3.25 grams) was also placed in a centrifuge tube and vibrated to settle the HA particles. The HA particles filled the centrifuge tube to a volume of 2.6 cc. The difference between these two volumes is the actual volume of $CaSO_4$ present, which is also the actual volume of $CaSO_4$ present, which is also the total volume of the implant which would resorb. The volume of $CaSO_4$ is 0.3 cc or 10.3% of the total volume. Therefore, after resorption of the $CaSO_4$ is complete, only 10.3% of the initial volume will have resorbed. Since tissue infiltration occurs simultaneously with calcium sulfate resorption, it is likely that there would be far less than 10.3% volume loss from the implant site. Thus, the implant site would be expected to maintain its post-operative-contour without a significant collapse.

EXAMPLE II

ANIMAL TESTS

A. Rabbits

Examining the bioresponse to calcium sulfate hemihydrate and hydroxylapatite composites began with a rabbit tibial defect model. Small holes penetrating to the medullary canal were cleaned of debris and left as unfilled controls, or were filled with a paste of HA-Composite, closed and allowed to heal.

The bone was labeled with oxytetracycline before sacrifice at 2 and 4 weeks. The undecalcified sections were photographed with fluorescent light using appropriate filters.

At 2 weeks, empty control holes were incompletely bridged with trabecular bone growth originating mainly from the

endosteum. For the HA-Composite defect, all but the central third of the implant site was bridged with new bone.

At 4 weeks, in the control, trabecular bone bridged the defect at the cortical level only. New bone had not yet invested the central three quarters of the defect site. In contrast, the HA-Composite, in most sections, was completely bridging the defect site, at subcortical levels, with trabecular bone. Although not known with certainty, it appeared that the composite had in fact enhanced the rate of bone growth. Higher magnifications showed the intimate nature of contact between the HA and new bone.

In rabbits, the HA-Composite accelerated trabecular bone bridging of the defect. This could not occur if the material were not biocompatible nor if the calcium sulfate were not easily resorbed and readily replaced by bone.

B. Dogs

This study was designed to ascertain the value of the HA-Composite in maintaining alveolar ridge morphology after tooth extraction. Previous studies had shown that if sufficient HA particles were retained in tooth sockets that ridge maintenance would result. The difficulty has been consistently retaining an adequate fill of particles by preventing particle exfoliation.

Maxillary and mandibular incisors and premolars were extracted from beagle dogs and filled with HA-Composite. Gingiva were approximated with sutures and never completely closed. No significant implant loss was observed for the 96 HA-Composite sites. The gingiva closed over the implant and control sockets within 7-10 days post-operatively. No incidence of inflammation or infection was observed. Gross examination showed

excellent retention of the implant, bony ingrowth and normal gingiva.

Once applied, the HA/$CaSO_4$ paste hardened in place in 15-30 minutes. The calcium sulfate gradually degraded in the body and concurrently the HA particles were invaded with tissue.

While particular embodiments of the invention have been described, it will be appreciated that a variety of changes and modifications can be made without departing therefrom.

WHAT IS CLAIMED:

1. A moldable bone-implant material comprising a cohesive plastic mixture of hard filler particles and a biocompatible, inorganic biodegradable binder.

2. The material of Claim 1, wherein the particles are hydroxylapatite.

3. The material of Claim 1, wherein the binder constitutes less than about one-third of the material's total volume.

4. The material of Claim 3, wherein the binder is biodegradable over a period of about three days to six weeks, with the material operatively placed in a bone site.

5. The material of Claim 4, wherein the binder is an inorganic cement.

6. The material of Claim 5, wherein the inorganic cement comprises calcium sulfate hemihydrate.

7. The material of Claim 1, comprising calcium sulfate hemihydrate and hydroxylapatite in the dry weight proportions of from about 15 to about 60% calcium sulfate hemihydrate and from about 40 to about 85% hydroxylapatite in admixture with sterile, biocompatible aqueous liquid to give a cohesive, moldable mass.

8. The material of Claim 7 wherein the dry weight proportions are from about 30 to about 40% calcium sulfate hemihydrate and from about 70 to about 60% hydroxylapatite.

9. The material of Claim 7 wherein the sterile, biocompatible aqueous liquid is sterile saline.

10. The material of Claim 7 wherein the sterile, biocompatible aqueous liquid is sterile water.

11. The material of Claim 2 wherein the particles of hydroxylapatite have particle sizes of from about 250 microns to about 5000 microns.

12. A storable, dry bone implant material comprising an intimate admixture of from about 15 to about 60% by weight of powdered calcium sulfate hemihydrate and from about 40 to about 85% by weight of hydroxylapatite particles.

13. The material of Claim 12 wherein the particles of hydroxylapatite have particle sizes of from about 250 microns to about 5000 microns.

14. The material of Claim 13 consisting essentially of from about 30 to about 40% by weight of powdered calcium sulfate hemihydrate and from about 60 to about 70% by weight of hydroxylapatite particles.

15. A method of filling a bone site with a contour-fitting, rigid-particle bone implant, comprising

providing hard filler particles in the form of a moldable plastic bone-implant material composed of a cohesive plastic mixture of the particles and a biocompatible, biodegradable inorganic binder; and

filling the bone site with the moldable material to form a contour-fitting implant at the site;

where gradual biodegradation of the binder and concommittment ingrowth of surrounding tissue acts to rigidify the implant over a period of several weeks.

16. The method of Claim 15, wherein the hard filler particles comprise hydroxylapatite.

17. The method of Claim 15, wherein the binder is inorganic cement.

18. The method of Claim 15, wherein the binder comprises calcium sulfate hemihydrate and the filler particles comprise hydroxylapatite particles.

19. The method of Claim 15, wherein the binder consists of calcium sulfate hemihydrate and the filler particles consist essentially of hydroxylapatite particles having a particle size of from 250 microns to about 5000 microns.

20. The method of Claim 15, wherein the providing hard filler particles in the form of a moldable plastic bone-implant material comprises mixing calcium sulfate hemihydrate and hydroxylapatite particles with an amount of sterile biocompatible aqueous liquid sufficient to form a moldable plastic mass.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 87/00548

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 L 27/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	NL, A, 8304129 (K. DE GROOT) 1 July 1985 see page 1, lines 24-25; claims 1-3 --	1-20
P,X	US, A, 4619655 (J.S. HANKER et al.) 28 October 1986 see the whole document --	1-20
P,X	Chemical Abstracts, volume 106, no. 6, 9 February 1987, (Columbus, Ohio, US), J.S. Hanker et al.: "Composite plaster/hydroxylapatite implants for jaw bone restoration", see page 356, abstract 38431m, & Mater. Res. Soc. Symp. Proc. 1986, 55(Biomed. Mater.), 77-96 --	1-20
X	EP, A, 0159089 (STICHTING BIOMATERIALS SCIENCE CENTER) 23 October 1985 --	1,3-6,9,10, 15,17
A	Chemical Abstracts, volume 80, no. 2, 14 January 1974, (Columbus, Ohio, US), J.W. Frame et al.: "Effects of sterilization on the properties ./.	

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26th June 1987	24 JUL 1987
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	of calcium sulfate hemihydrate", see abstract no. 6891q, & J. Appl. Chem. Biotechnol. 1973, 23(7), 493-500	1,6

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 87/00548 (SA 16684)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 07/07/87

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
NL-A- 8304129	01/07/85	None	
US-A- 4619655	28/10/86	None	
EP-A- 0159089	23/10/85	NL-A- 8401061	01/11/85

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82